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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/806,793	03/22/2004	Teit E. Johansen	19313-001CON	2372

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EXAMINER	
BALLARD, KIMBERLY A	
ART UNIT	**PAPER NUMBER**
1649	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/26/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/806,793	JOHANSEN ET AL.	
	Examiner	Art Unit	
	Kimberly A. Ballard	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *66-85* is/are pending in the application.

4a) Of the above claim(s) *66-79* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *80-85* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/347,613.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/29/04, ~~4/7/05~~, 9/11/06*. 6-17-05
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

Claims 1-65 were cancelled and claims 66-86 were added in the third preliminary amendment filed February 7, 2006. In the amendment filed January 22, 2007, Applicant cancelled claim 86 and amended claims 80 and 84-85. Following the amendments, claims 66-85 are pending in the current application.

Election/Restrictions

Applicant's election with traverse of Group XXIX, claims 80-86, drawn to a method of treating or preventing a disorder of the eye, comprising administering a cell line expressing a Neublastin polypeptide of SEQ ID NO: 12, in the reply filed on January 22, 2007 is acknowledged. The traversal is on the ground(s) that SEQ ID NOS: 10, 11, and 12, Applicants note, are truncated versions of the pre-pro-Neublastin polypeptide recited in SEQ ID NO: 9. Applicants therefore assert that any search for peptides comprising the amino acid sequence of SEQ ID NO: 12 will necessarily find SEQ ID NOS: 9-11. Applicants submit that the inventions of Groups XXVI-XXIX can be searched at the same time without undue burden on the Examiner, and therefore request withdrawal of the Restriction Requirement with respect to Groups XXVI-XXIX. This is found persuasive, and accordingly, the Restriction Requirement with respect to Groups XXVI-XXIX is hereby withdrawn. However, the remaining groups, namely Groups I-XXV and XXX, are still independent or distinct inventions from the elected invention of Groups XXVI-XXIX (directed to a treatment method using SEQ ID NOs: 9-

12), as was set forth in the previous office action mailed November 21, 2006. Therefore, the requirement for restriction between the inventions of groups (XXVI-XXIX) and (I-XXV and XXX), and also between each of groups (I-XXV and XXX) is maintained for reasons of record.

The requirement is still deemed proper and is therefore made FINAL.

Claims 66-79 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on January 22, 2007.

Claims **80-85**, drawn to a method of treating or preventing a disorder of the eye, comprising administering a cell line expressing a Neublastin polypeptide of SEQ ID NOS: 9-12, are under examination in the instant office action.

Information Disclosure Statement

Signed and initialed copies of the IDS papers submitted November 29, 2004, June 17, 2005, and September 11, 2006 are enclosed in this action. The IDS paper submitted February 20, 2001, however, is in improper form and does not comply with 37 CFR 1.98 (a)(1)(ii), see also MPEP § 609, and therefore has been lined through. Applicant is required to resubmit a clean, complete reproduction of the February 20, 2001 IDS for consideration by the Examiner.

Claim Objections

Claims 81 and 82 are objected to because of the following informalities: The claims recite that the claimed polypeptide comprise specific amino acid residues at specific positions when numbered in accordance with SEQ ID NO: 2. However, SEQ ID NO: 2 is a non-elected sequence. The Examiner suggests amending the claims to reflect numbering the recited conserved amino acids in accordance with one of the elected sequences, such as SEQ ID NOs: 9-12. Appropriate correction is required.

Sequence Requirements

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). This application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825. For example, 37 CFR 1.821(d) requires the use of the assigned sequence identifier (i.e., SEQ ID NO: X) in all instances where the description or claims of a patent application discuss sequences regardless of whether a given sequence is also embedded in the text of the description or claims of an application.
Instant claim 83 recites amino acid sequences (e.g., LGLG, FRFC, QPCCRP, and SATACGC) that are encompassed by the definition for amino acid sequences, and therefore require sequence identifiers. Applicant is also reminded to check the entire disclosure to ensure that the application is in sequence compliance.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed provisional applications, Application Nos. 60/092,229 (filed 07/09/1998), 60/097,774 (filed 08/25/1998), and 60/103,908 (filed 10/13/1998), fail to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. The provisional applications do not disclose the instantly claimed method of treating or preventing a disorder of the eye comprising administering a cell line expressing a Neublastin polypeptide. Support for the instantly claimed method is first noted in the non-provisional Application No. 09/347,613, filed 07/02/199, now US Patent No. 6,593,133, particularly at column 20, lines 56-57 and column 21, lines 46-51. Accordingly, for purposes of prior art, the effective filing date of the instant claims is **02 July 1999**.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 80-85 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating photoreceptor loss in the retina of patients afflicted with macular degeneration, retinitis pigmentosa, or glaucoma, comprising administering to the eye of said patient a cell line expressing a Neublastin polypeptide, wherein said polypeptide comprises one of the amino acid sequences selected from the group consisting of SEQ ID NOs: 9-12, does not reasonably provide enablement for a method of prevention as broadly claimed or a method of treating *any* disorder of the eye comprising administering a cell line expressing a Neublastin polpeptide, which comprises an amino acid sequence that is at least 90% or 95% homologous to the amino acid sequence of SEQ ID NO: 12. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims. *In re Wands*, 8 USPQ2d, 1400 (CAFC 1988).

The (rejoined) claims are broadly drawn to a method of treating or preventing a disorder of the eye comprising administering to the eye of an individual suffering from said disorder, a cell line expressing a Neublastin polypeptide, which comprises an amino acid sequence that is at least 90% homologous (or 95% homologous) to an amino acid sequence selected from the group consisting of SEQ ID NOs: 9, 10, 11, and 12. Thus, the claims broadly encompass the use of cells expressing a genus of molecules to treat or prevent a genus of eye disorders.

The nature of the invention is the characterization of a GDNF-like neurotrophic factor called "neublastin" (also known in the art as Artemin or Enovin) and the demonstration that neublastin is capable of enhancing the survival of cultured neural cells, such as dorsal root ganglia (DRG) cells (Example 8). Applicant additionally demonstrates that the survival of embryonic dopaminergic mesencephalic neurons co-cultured with transfected neublastin-producing HiB5 cells was significantly increased compared to dopaminergic cells co-cultured with non-transfected HiB5 control cells (Example 7).

At the time of the invention, the art recognizes the ability of neurotrophic agents (such as CNTF, BDNF, neurotrophin-4, GDNF, etc.) to protect photoreceptor cells of the retina from degenerating conditions (see, for example, LaVail et al. (1998) *Invest Ophthalmol Vis Sci.* 39(3): 592-602). Along these lines, the art clearly acknowledges Artemin (i.e., Neublastin) as a member of the GDNF family, and its capability to support the survival of dopaminergic midbrain neurons in culture (see Baloh et al. *Neuron*, 1998; 21:1291-1302) The art further recognizes that intraocular transplants containing retinal

pigment epithelium (RPE) cells are able to rescue photoreceptor cells from degeneration caused by, for example, age-related macular degeneration (see Algvere et al. *Graefe's Arch Clin Exp Ophthalmol.* 1997; 235: 149-158; and Little et al. *Invest Ophthalmol Vis Sci.* 1996; 37(1): 204-211).

Applicant's invention is thus predicated on the finding that Neublastin is a neurotrophic agent. Applicant extrapolates this finding into a method of treating or preventing an eye disorder, comprising administering to the eye of a patient suffering from said disorder a cell line expressing a Neublastin polypeptide that is 90% or 95% homologous to one of SEQ ID NOs: 9-12. However, no specific guidance, prophetic or otherwise, is provided demonstrating that a Neublastin polypeptide that is 90 or 95% homologous to one of SEQ ID NOs: 9-12 is capable, either *in vitro* or *in vivo*, of supporting the survival of degenerating photoreceptor cells, and in the process treat a disorder of the eye. The polypeptide of SEQ ID NO: 9 is a 220 amino acid sequence designated pre-pro-Neublastin. Applicant has identified three variants of SEQ ID NO: 9 including a 140 amino acid polypeptide designated NBN140 (SEQ ID NO: 10), a 116 amino acid polypeptide designated NBN116 (SEQ ID NO: 11), and a 113 amino acid polypeptide designated NBN113 (SEQ ID NO: 12). All of these sequences comprise SEQ ID NO: 12, and thus all sequences are 100% homologous to each other. Applicant fails to provide sufficient evidence or guidance of other Neublastin polypeptides that are 90-95% homologous to the Neublastin sequences of SEQ ID NOs: 9-12. The claims are therefore overly broad in the recitation of "at least 90 or 95% homology" since insufficient guidance is provided as to which of the myriad of amino acid species

encompassed by the claims will retain the characteristics of being neurotrophic agents for the treatment of photoreceptor loss.

Moreover, the specification lacks guidance as to whether the method would be efficacious for the treatment of an eye disorder besides those resulting from photoreceptor loss (i.e. macular degeneration, retinitis pigmentosa, or glaucoma). It would not be expected that the present invention could treat or prevent, for example, dry eyes or cataracts, which are both disorders of the eye.

Furthermore, "prevention" is understood in the art to encompass total protection from disease or injury. Thus, given the high level of required effect, a high level of evidence showing prevention is also required. The instant specification, however, fails to teach that the administration of a cell line expressing a Neublastin polypeptide is capable of treating any eye disorder, and in no way demonstrates prevention of eye disorders.

While the skill level in the art is high, the level of predictability with respect to treatment of photoreceptor loss is low. The art recognizes that while transplantation of RPE cells or photoreceptor cells holds promise as a treatment for restoring vision in the eye, immunological rejection of transplanted material is one of the main reasons why retinal transplantation has not yet proved successful (see Enzmann et al. *Acta Anat.* 1998; 162:178-183). Addtionally, the art recognizes that there are no treatments or preventive measures currently available for patients with particular neurodegenerative eye disorders, such as dry macular degeneration (see US Patent 6,361,771 B1 to Tao et al., paragraph spanning columns 22-23). Tao et al. further teach that retinitis

pigmentosa is a genetic disorder that causes the degeneration of cells in the retina (column 23, lines 11-13). It is therefore unlikely that that the claimed method would be able to "prevent" an inherited disease.

Thus, it would require undue experimentation to use cell lines expressing Neublastin homologous polypeptides in a method of treating or preventing photoreceptor loss, particularly when functional evidence regarding Neublastin homologs is lacking. And even assuming *arguendo* that the specification was enabling for a method of treating or preventing photoreceptor loss, it would still not be enabled for a method of treating or preventing any disorder of the eye using the full scope of Neublastin homologs for the reasons set forth above.

Therefore, in view of the breadth of the claims encompassing polypeptide homologs of unknown efficacy, the lack of adequate guidance or working examples on the use of cell lines expressing these polypeptides for the support or rescue of retinal cells, the lack of sufficient guidance or data or evidence supporting a preventative effect of the claimed method, the unpredictability in the art of retinal transplantation methods, and the complex nature of the invention, one of skill in the art would find that undue experimentation would be required to practice the claimed invention.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 80-85 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "preventing a disorder of the eye comprising administering to the eye of an individual suffering from said disorder" in claim 80 is ambiguous and indefinite because it is not clear how it is possible to *prevent* a disorder in a patient *already suffering* from the disorder. The metes and bounds of the claim thus cannot be ascertained.

Claims 81-85 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for being dependent from indefinite rejected claim 80.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 80-85 are rejected under 35 U.S.C. 102(b) as being anticipated by Algvere et al. (*Graefe's Arch Clin Exp Ophthalmol.* March 1997; 235: 149-158).

Claims 80-85 are drawn to a method of treating or preventing a disorder of the eye comprising administering to the eye of an individual suffering from said disorder, a cell line expressing a Neublastin polypeptide, which comprises an amino acid sequence that is homologous to the amino acid sequence of SEQ ID NO: 12, and wherein the disorder includes photoreceptor loss in the retina in patients afflicted with macular degeneration, retinitis pigmentosa, or glaucoma.

Algvere et al. teach transplantation of human retinal pigment epithelial (RPE) cells to patients with age-related macular degeneration (AMD). Specifically, Algvere notes that both patches of human fetal RPE as well as suspensions of RPE cells were transplanted into the subretinal space of patients with AMD (see "Material and Methods" p. 150-151). Although Algvere et al. are silent with respect to Neublastin polypeptides of SEQ ID NOs: 9-12, it would be an expected property of the transplanted fetal retinal cells to inherently express such polypeptides, as the instant application evidences at pages 44 and 46 of the specification, which demonstrates that neublastin is expressed in retina of both embryonic and postnatal rodents. The Neublastin polypeptides expressed on the RPE transplants would similarly be expected to at least 90% or 95% homologous to the claimed SEQ ID NO: 12, as well as inherently possess the conserved amino acids recited in claims 81 and 82 and the particular amino acid motifs of claim 83. Algvere et al. further report that RPE cell suspension transplants were well-tolerated by the host (i.e., showed no evidence of rejection), were associated with reduced AMD pathology (e.g., disappearance of retinal deposits called "drusen") and

improved visual function (see pp. 153-155). Accordingly, the method disclosed by Algvere et al. would fully anticipate the instantly recited method of claims 80-85.

Claims 80-85 are rejected under 35 U.S.C. 102(e) as being anticipated by US 2003/0059868 A1 by Greenwood et al., published March 27, 2003, priority to January 22, 1998.

Greenwood et al. disclose the use of retina-derived (retinal endothelial or retinal epithelial pigment) cells lines for implantation in the retina, wherein the cell lines carry a therapeutic substance to the eye (see abstract). For example, Greenwood et al. teach the rescue of visual function by transplantation of human retinal pigment epithelial cells to the retinae of RCS (Royal College of Surgeons) rats, which are an art-accepted animal model of age-related macular degeneration (see [0150]). Greenwood et al. further teach that the cell lines may be transfected so that they express a specific therapeutic polypeptide in the eye, such as Neublastin (see claims 16-18). Although the sequence Neublastin is not given, it would be an expected property of the Neublastin polypeptide disclosed by Greenwood et al. to be 100% homologous to the instantly claimed amino acid sequences, and would therefore comprise the recited conserved amino acids and motifs of instant claims 81-83. Accordingly, Greenwood et al. teach a method of administering a cell line expressing Neublastin for treatment of eye disorders, such as macular degeneration, which would anticipate instant claims 80-85.

Claims 80-85 are rejected under 35 U.S.C. 102(e) as being anticipated by US Patent 6,361,771 B1 to Tao et al., issued March 26, 2002, priority to April 6, 1999.

Tao et al. disclose the ARPE-19 cell line, which is viable in central nervous system and intra-ocular environments, for cell-based delivery technology (see abstract). Tao et al. teach that transplantation of ARPE-19 cells is useful for administering a desired therapy factor for treating neurodegenerative diseases (see column 23, lines 44-46), wherein the ARPE-19 cells are genetically modified to secrete a desired therapeutic factor (column 23, lines 51-53). Tao discloses that the retina is a site subject to chronic degeneration, and further teaches age-related macular degeneration, retinitis pigmentosa and diabetic retinopathy as the major disorders of the eye leading to retinal degeneration (see column 22, line 41 – column 23, line 28). Tao thus discloses the treatment of retinal degeneration using ARPE-19 cells designed to secrete neurotrophic factors (see column 23, lines 33-37 and column 2, lines 14-18). The therapeutic factor secreted by the genetically modified ARPE-19 cells include, but are not limited to Neurturin (NTN), Neublastin, GDNF, PDGF, CNTF, BDNF, etc. (see paragraph spanning columns 23-24 and claim 7). The Neublastin polypeptide disclosed by Tao et al. would be expected to be 100% homologous to the instantly claimed Neublastin sequences of SEQ ID NOs: 9-12. Accordingly, the disclosure by Tao et al. fully anticipates instant claims 80-85.

Conclusion

No claims are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly A. Ballard whose telephone number is 571-272-4479. The examiner can normally be reached on Monday-Friday 9AM - 5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Elizabeth C Kemmerer

Kimberly Ballard, Ph.D.
March 8, 2007

ELIZABETH KEMMERER
PRIMARY EXAMINER